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Short Communication

Metastases its Biologics and Impact in Internal Medicine

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Cancer Metastases (Mets), the dissemination and growth of tumor cells at distant sites of the primary tumor, is a very complex Biological and Clinical process, that when intractable, leads most of the times to the patient death. Mets are the Cancer paradigm and is still a "prohibited" word in many parts of the world´s societies [1,2]. Cancer adjuvant or metastases-preventing therapies, such as Chemotherapy (Chemo) and nowadays Immunotherapy (Immune) give impressive survival rates results.

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Since 40 to 50 years ago, we are observing how Chemotherapy cures many tumor types in the metastatic setting of the pediatric and adolescent patients' population, for e.g., such as leukemias, bone tumors, Kidney tumors and even special Central Nervous System (CNS) Cancers. There are milestones on the above-mentioned, Sidney Farber achievements with aminopterin (simile-Methotrexate) and the remissions in Acute lymphoblastic leukemias, the use of D-Actinomycin in Wilms tumors (renal infants Cancer) and their results with therapeutic ameliorations. We can continue mentioning, prominent Oncologists such as Joe Bertino and his works with Methotrexate, discovering how high doses of this drug can cure or relief metastatic osteosarcoma patients. A seminal stone was the cure of metastatic testicular Cancer by Lawrence Einhorn, with exceptional results with the possible-non nephrotoxic use of Cisplatin with hyperhydration to the before Chemo scheme; this was studied preclinically in dogs by Daniel Hayes and Esteban Cvitkovic. Testicular Cancer became the first solid tumor cured by Chemo [3].

Fifteen years later, the early development of Irinotecan by Professor Jean-Pierre Armand and his Team at Phase 1 Unit of the Institut Gustave-Roussy, was another seminal Oncology achievement. Irinotecan-based regimens became the backbone standard-of-care for the treatment of advanced metastatic Colorectal Cancer patients. On the other hand, and since the last decade, it has been observed with fascination tumor regressions and potential cures with the Immune-checkpoint inhibitors that work by the inhibition of the negative immune

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regulation, thus stimulating with these Immuno-Compounds (IC), the "lazy" tumor-killers-lymphocytes. Now the T killer Lymphocytes are "allowed" to eat tumors [4]. As an example, this can be mainly observed in advanced melanoma patients, that in the past were unresponsive to different Chemotherapy schedules (e.g., Dacarbazine) and maneuvers and that currently due to the checkpoint inhibitors Immunotherapy IC, more than 40% of the far advanced adult patients live more than 2 years and some of them get even cured. Impressive results, these patients presented with lung, liver, bone, and brain Mets, and even these lasts can disappear with IC. Modern Clinical Oncology is mainly guided by Immunotherapy (different types of it), and by the small molecules-targeted therapies, that present also exceptional antitumoral results in some of them and being really game-changer drugs.

Many Clinical Trials finished, with amazing results as already mentioned, and many Trials are on the road. These last ones comport the aid of Precision Medicine "to Tell" what IC or Drug is better to deliver, evaluate the tumor burden, the more one, the more clinical positive impact with the checkpoint inhibitor or IC. It is noteworthy that Mets are the main systemically treated part of the patient process, remaining the primary tumor site as treatable initially by Surgery, Radiotherapy, classic Chemotherapy, and Immunotherapy according to the initial bulk of disease present. The whole Mets process lacks a clear knowledge about primers and tumor drivers, and it has been studied very deeply with Genomics, Proteomics, Metabolomics, trying to catch drivers and other affected genes that could guide the conduct of the different metastatic phases. Whole tumor genomes are being studied and is interesting to mention that primary tumors have different gene patterns in relation to the Mets ones. This have enormous clinical interest, the best practice but sometimes with no adhesion from patients, are to also perform Mets biopsies after tumor relapses, so this has also been done in these tissues. The aim: to study patterns of the different biomarkers in the whole tumor genome and its therapeutic anticancer drugs sensitivity. The primary tumor is genotypically and phenotypically different from the Mets. Some Mets are more sensitive to Chemo for they growth rapidly, but in peculiar tumors, these rapid chemosensitivity is a precursor of a rapid relapse. This situation is not applicable to all metastatic Cancers fortunately, many Cancer Mets depending on the tumor biology, are cured for everlasting.

Tumor Mets biopsies at different evolutive tumor times are feasible in well-designed and well-conducted Clinical Trials, the patient here, must sign the Inform Consent, where a clear explanation of the need of different tumor biopsies are a must to do. Antimetastatic drugs entered in the past the clinical arena revealing marginal anticancer activity, they mainly interacted with the metalloproteinase's enzymes without any therapeutic success. But it is to mention that nowadays, are in the way elegant preclinical studies with antimetastatic Drugs, waiting to prove their worth in the clinical setting. The whole Mets process comports a first chapter that is the cell tumor shedding from the primary site, then, their extravasation by crossing vascular and lymphatic capillaries and this is followed by the circulating tumor cells (CTC) in the bloodstream. Posteriorly and last, the tissue invasion takes place, where the Mets arrive to the interstitial connective tissue as seeds, interacts with it and begin to growth as "round balls" everywhere. It must mention in relation to the above, that CTC represent a very small fraction of the primary tumor cells (extremely selective evolutive trait), with the fact that most of them will die in the bloodstream due to their impacts to big vessels and mechanical fluids dynamics sometimes not favorable (noteworthy is the fact that only 1 % of the CTC remain

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with metastatic potential), so only a minority colonize the extracellular matrix site, these cells won the selective pressures and conduct now the events [5,6]. This environment is also hostile mainly due to an acidic pH which makes to the cells a metabolic turn and the obtention of their energy for growth from the anaerobic glycolysis mainly (Warburg effect) and with some compound's amino acid-derived, that are in the process and play a role. The interactions for seeding and growth are due to their interaction with the tumor microenvironment (TME) that is the interstitial connective tissue with fibroblasts, immune cells, the surrounding blood and lymphatic vessels, macrophages that depending on their "mood", they can "eat" Mets, or they can help Mets in their growth.

The whole metastatic cascade is according to the afore mentioned with an enormous complexity for: 1. Tumor shedding is not a druggable target at the present time, 2. tumor extravasation neither, 3. the killing of Circulating Tumor Cells (CTC) (with current detectable and prognostic biomarkers) are druggable and [4]. we are beginning to dissect the signal molecules to develop TME-acting-drugs and bring them into the clinical arena. It can describe some type of primary tumors with high volume ones with "marginal metastatic potential" and others a with lesser volume, that always present overt Mets. As per today, it has been known that Mets is initially a microscopically early event that can be programmed to rest in the Go gap of the cell cycle for long periods of time before the clinically manifested disease, e.g., the apparition Breast Cancer Mets, 10 years or more after initially curative maneuvers (Surgery, Radiation Therapy, Chemo, anti HER2 agents, Hormonotherapy). This non-dividing gap of the cell cycle(Go) is permeable to the worth of adjuvant preventing-metastatic-therapies (adjuvant Chemo) that are to check-maintain or destroy these tumor microdeposits. These cell tumor niches are mainly present in the bone marrow, a perfect and comfortable rest site for micro-Mets. Unknown endogenous messengers can modify this rest status, and cells niches enter in the next cell cycle phases and begin to divide, conforming Cancer clones and migration from the bone marrow to other also "comfortable soils".

At the present time, it has been treated overt Mets, bulky initial not surgical primary tumor sites (neo-adjuvant Chemo or Immune) and "elegantly" the micro metastatic disease (adjuvant therapy). So please, don´t be so ambitious! these are milestones in Cancer therapy.

Well, known is Dr Paget´s theory about the seed and soil of metastases.

Not every soil is permeable to be colonize by metastatic cells. The biochemical signals are beginning to being known nowadays, and many proteins are being individualized. These cells won the selective pressures in the TME and conduct now the metastatic events. As already mentioned, it hasn't known much about tumor drivers in Mets, but in counterpart, clonality is the essential aspect to consider. Tumors are clonal and this heterogeneity are the main phenotypic trait that drives clone's Mets-genesis [7]. Very old and well-known is the fact that there are patterns for the metastatic disease, depending on the tumor primary sites [3]. For e.g., Breast Cancer can give metastases to the lymph nodes primarily, and then hematogenous to the liver, lungs, bones, brain. HER2 positive Cancers have the more frequent brain Mets within the spectrum of Breast Cancers. Prostate Cancer is mainly a metastatic bone disease, and colorectal Cancer, a liver and peritoneal metastatic disease.

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It is probable that an early development metastatic program exists with strong migratory aspects and with the "green light" of "don´t cease the tumor growth" at different organ sites [8].

It can be imagined that sometimes Mets are difficult-to-treat, for there are no Cancer specific processes: for e.g. Mets have similar traits to the migration of neutrophils from blood to the connective interstitial tissue; inflammation and wounds healing comport similar aspects with Mets, it can be considered Cancers as "wounds that do not heal"!, and even the coagulation clotting system cascade is involved in the metastatic process (platelets help with tissue adhesions). So, it is still not totally selective, for with the knockout of the "all" before mentioned nonspecific processes, many kinds of organ-related toxicities arrive.

It must be dissected with Genomics, more and more Mets "anatomy and physiology" to find key driver processes or many passengers genes that could help in it and that can be tackled. In the case if it's not comfortable with the still "putative" drivers, the zone-to-go are the Transcription Factors (TFs), rooms cell operators and bottle necks of driver mutated genes [9]. Blocking one of the TFs, it can indirectly touch many sick and probably driver genes. Buteven many novel anti-TF drugs are in different Pharmacology development Phases, these TF are currently still "quite elusive foes".

It can also dream about the discovery of anticancer drugs that can act at the metastatic cascade in some way like the Angiotensin-converting enzyme (ACE) inhibitors. The targetable anatomy of the ACE receptor is fascinating, once this receptor is touched by some peculiar antihypertensive drugs, the most sensitive part of the arterial hypertensive process is corrected. Really a great unique target! But again, the problem is still here: Cancer Mets cascade is more complex than the hypertension process, so the take-home-message is that anti-metastatic-cascade compounds development is a challenging task, but this can raise a big interest to the pharmaceutical industry of an area of drug research, that finally would bring us outstanding novel drugs into the clinical setting.

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